Effect of Setmelanotide (MC4R Agonist) on Obesity and Hunger in Individuals With Alström Syndrome

T-P-3429

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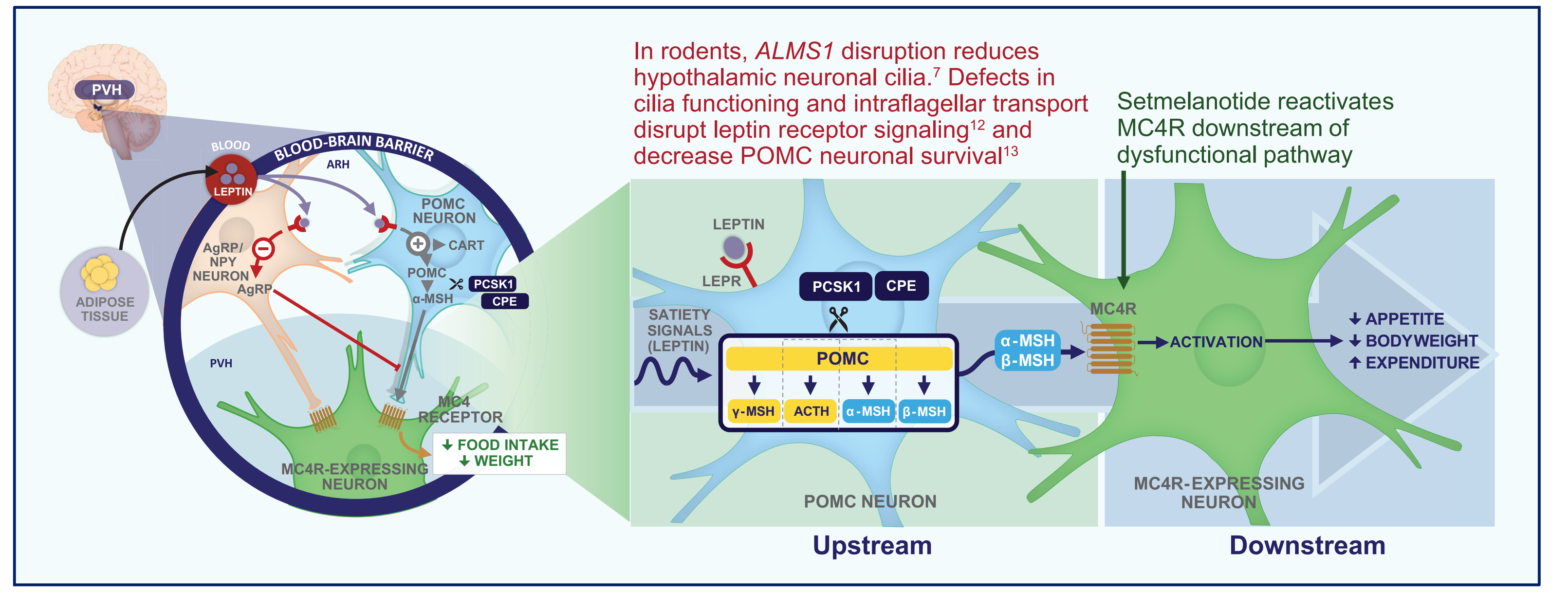
Summary

- **Updated data from individuals with Alström syndrome enrolled in a phase 2 basket study suggest that treatment with setmelanotide reduces body weight and hunger scores**
- **The safety profile of setmelanotide in Participants with Alström syndrome is consistent with that of previous studies of Participants receiving setmelanotide[1-3]**
- **These results support the further investigation of setmelanotide in rare genetic disorders of obesity involving the melanocortin-4 receptor (MC4R) pathway, including Alström syndrome, *POMC* and *LEPR* mutations, and Bardet-Biedl syndrome (BBS); genotype-specific responses also need to be explored**

Introduction

- Alström syndrome is a rare genetic ciliopathy characterized by early-onset severe obesity, hyperphagia, retinal dystrophy, sensory hearing loss, cardiomyopathy, and metabolic conditions[4,5]
  - Preclinical data may suggest that cilia play a role in the MC4R pathway, a component of the central melanocortin pathway, which regulates energy balance and body weight (Figure 1)[6-8]
- In phase 2 studies of the MC4R peptide agonist setmelanotide in individuals with *POMC* and *LEPR* mutations and BBS, setmelanotide was safe and reduced body weight and hunger scores[1,2]
- The effect of setmelanotide in individuals with Alström syndrome is being investigated in an ongoing phase 2 study (ClinicalTrials.gov identifier, NCT03013543), and a previous report[9] showed that setmelanotide reduced body weight and hunger scores, improved other metabolic parameters, and had a safety profile consistent with prior phase 2 studies[1,2]

Figure 1. The MC4R pathway is a component of the central melanocortin pathway; it regulates appetite and energy balance, and mutations in this pathway may result in rare genetic disorders of obesity.[8,10,11]



ACTH, adrenocorticotropic hormone; AgRP, agouti-related protein; ALMS1, Alström syndrome protein 1; ARH, arcuate nucleus; BBS, Bardet-Biedl syndrome; CART, cocaine- and amphetamine-related transcript; CPE, carboxypeptidase E; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; PCSK1, pro-protein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; PVH, paraventricular nucleus of hypothalamus.

Objective

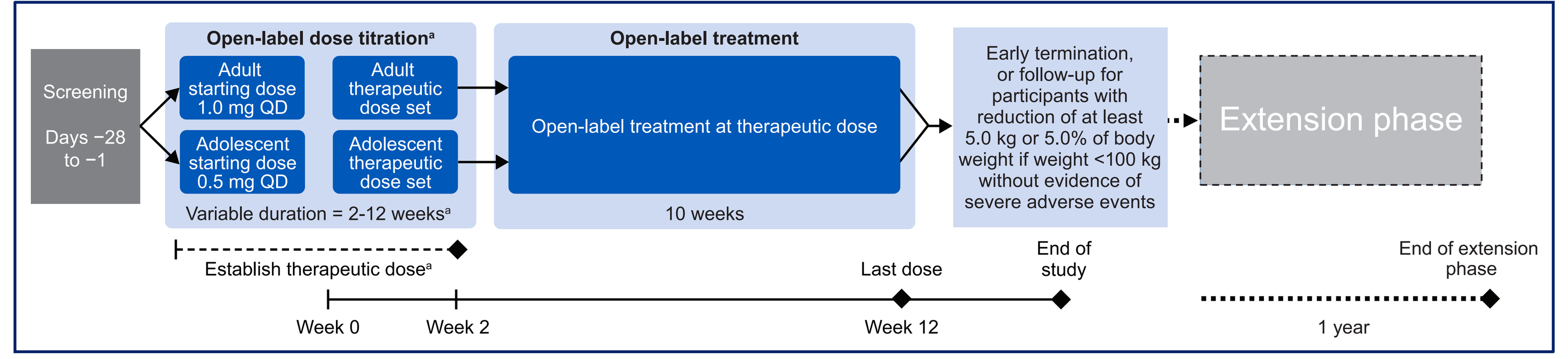
- To report updated data on the effects of setmelanotide on body weight, hunger scores, and safety in 4 individuals diagnosed with Alström syndrome participating in an ongoing phase 2 study of setmelanotide

Methods

Study Design and Participants

- This is a phase 2, interventional, open-label, single-arm study enrolling individuals aged ≥12 years with a genetically confirmed diagnosis of a rare genetic disorder of obesity, including Alström syndrome (Figure 2)
  - Participants aged ≥18 years have a body mass index ≥30 kg/m²
  - Participants aged ≥12 to <18 years have weight >97th percentile for age/sex on a growth chart
- Participants with >2.0% weight loss from intensive diet or exercise regimens within 2 months of enrollment or >10.0% weight loss that was durably maintained after gastric bypass surgery are excluded

Figure 2. Phase 2 basket study design and treatment duration.



QD, once daily. [a]The last 2 weeks of the open-label dose titration phase in which the optimal therapeutic dose for a participant is established is considered the first 2 weeks of the open-label treatment phase. Participants then receive an additional 10 weeks of active treatment in the open-label treatment phase for a total of 12 weeks of treatment at the therapeutic dose.

Endpoints

- The primary endpoint is the percent change in body weight after 12 weeks at therapeutic dose
- Secondary endpoints include safety, tolerability, and changes in hunger score and weight at 6 and 12 months post baseline

Assessments

- Body weight, blood pressure (BP), and heart rate are recorded at each visit
  - 24-hour ambulatory BP monitoring was performed for Participants 1 and 2
  - Body composition (as assessed by InBody 770, InBody, Seoul, South Korea); skin and physical examinations; and metabolic, endocrine, and hematologic testing are also conducted at regular intervals
- Resting energy expenditure is measured by indirect calorimetry (TrueOne 2400, Parvo Medics, Sandy, UT), with percent predicted calculated using the Mifflin–St. Jeor equation[14]
- Hunger scores are recorded daily by the participant using the following questionnaire, with each item scored on a Likert-type scale in which 0 equals no hunger at all and 10 equals most hunger:
  - "In the last 24 hours, how hungry did you feel when you were the most hungry?"
  - "This morning when you woke up for the day, how hungry did you feel?"
  - "In the last 24 hours, on average, how hungry did you feel?"

Results

Participants and Baseline Characteristics

- 4 Participants with Alström syndrome were enrolled (Table 1)
  - Participants 1, 2, and 4 received setmelanotide treatment at therapeutic dose for 50, 36, and 27 weeks, respectively, as of October 2018; Participant 3 discontinued treatment before completing 12 weeks of treatment on therapeutic dose due to early withdrawal of consent

Table 1. Baseline Characteristics of Participants With *ALMS1* Mutations

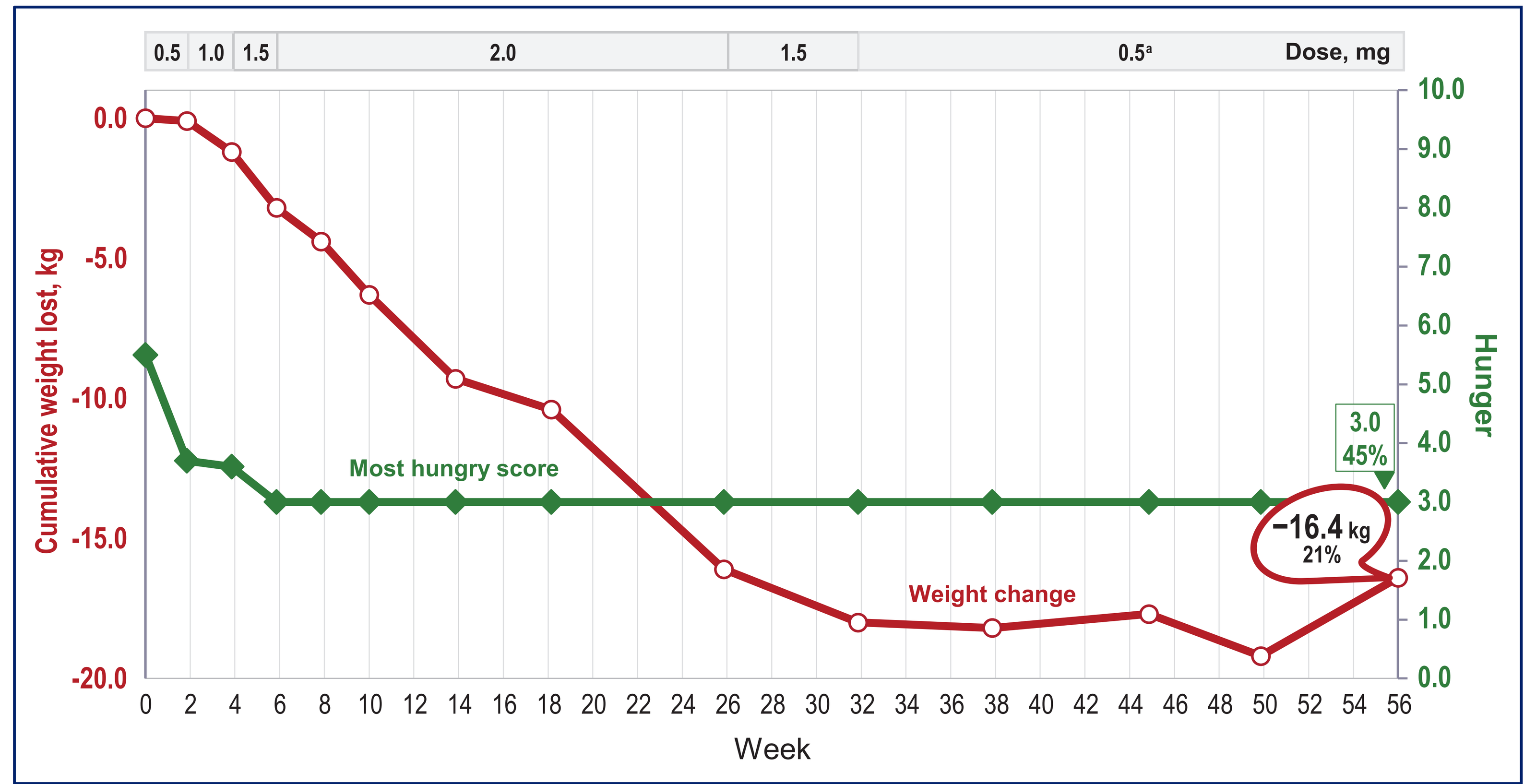
Participant	Age, y/Sex	*ALMS1* mutation
1	12/M	Chromosome 2 uniparental disomy with homozygous: c.4156dupA > p.Thr1386AsnFS*15
2	15/F	Compound heterozygous 9328C>T (gin3110*) and 10549C>T (gin3517*)
3 (discontinued)	21/F	Compound heterozygous c.10579_10580delAT; p.Met3527ValFS*13 and c.11856delC; p.Asn3952LysFS*41
4	16/F	Compound heterozygous c.4148C>G; p.Ser1383X and c.0991C>T; p.Gln3001X

F, female; M, male.

Efficacy

- At the primary endpoint (after ~12 weeks on therapeutic dose), percent weight losses in Participants 1, 2, and 4 were 13.2%, 5.7%, and 5.5%, respectively, and most-hungry scores were reduced in Participant 1 and 2 from 5.5 to 3.0 and from 6.9 to 1.9, respectively, whereas the most-hungry score increased in Participant 4 from 4.1 to 5.0
- Longer-term data (beyond the primary endpoint) demonstrated reductions in body weight, and Participants 1 and 2 also demonstrated reductions in hunger scores and improvements in body composition and metabolic parameters (Tables 2 and 3; Figure 3)[9]
  - Notably, substantial reductions in glycated hemoglobin and triglycerides were observed in Participant 2

Figure 3. Weight and hunger scores over time for treatment beyond 1 year (Participant 1).



[a]Dose was decreased to 0.5 mg for 6 days/week at Week 50.

Safety

- Adverse events (AEs) associated with setmelanotide treatment included increased pigmentation of the skin/nevi and injection-site reactions
  - No serious AEs or discontinuations due to AEs were reported
- No clinically significant increases in BP were observed that resulted in the development of hypertension (Table 2)

Table 2. Changes in Parameters From Baseline to Last Observation

Measure	Participant 1	Participant 2	Participant 3	Participant 4
Last observation, week including titration period	56	46	15	20
Baseline [Current] weight, kg	78.6 [62.2]	70.7 [66.9]	108.1 [107.0]	91.6 [86.6]
Weight change from baseline, %	−20.9%	−5.4%	−1.1%	−5.5%
Baseline [Current] BMI, kg/m²	27.8 [22.0]	31.4 [29.5]	47.4 [46.9]	35.4 [32.6]
BMI change from baseline, %	−20.9%	−6.1%	−1.1%	−7.8%
Baseline [Current] (BP mean of 3 measurements), mm Hg	120/86 [99/69]	107/73 [103/68]	96/40 [117/57]	126/70 [118/77]
Baseline [Ending] average hunger score, points	4.1 [3.0]	5.4 [1.1]	7.2 [8.5]	3.8 [5.0]
Baseline [Ending] morning hunger score, points	4.1 [3.0]	8.3 [1.1]	3.5 [2.5]	3.4 [2.0]
Baseline/Ending most hungry score, points	5.5 [3.0]	6.9 [2.3]	7.9 [8.7][a]	4.1 [5.0]
Change in most hungry score, %	−45.5%	−66.7%	−10.1%	22.0%

BMI, body mass index; BP, blood pressure. [a]Measurement taken at Week 10.

Table 3. Changes in Body Composition, Endocrine, and Metabolic Parameters From Baseline in the 2 Participants With at Least 6 Months of Treatment

	Participant 1		Participant 2	
Measure	Baseline [Week 56] value	Percent or absolute change	Baseline [Week 46] value	Percent or absolute change
Height, cm	168.1 [168.2]	0.1%	150.0 [150.5]	0.3%
BMI percentile	97.8 [83.6]	−14.6%	97.2 [95.2]	−2.1%
Waist circumference, cm	102.4 [83.0]	−18.9%	97.4 [93.5]	−4.0%
Hip circumference, cm	104.6[a] [91.9]	−12.1%	96.4[a] [92.3]	−4.3%
Neck circumference, cm	36.0[a] [33.4]	−7.2%	37.3[a] [37.0]	−0.8%
Body fat, %	29.8 [19.3]	−35.2%	42.0 [37.3]	−11.2%
ALT, U/L	120 [105]	−13%	26 [27]	4%
AST, U/L	71 [57]	−20%	25 [20]	−44%
Triglycerides, mg/dL	164 [84]	−49%	1039 [231]	−78%
HDL, mg/dL	44 [61]	39%	29 [37]	28%
LDL, mg/dL	127 [70]	−45%	61 [123]	102%
HbA_{1c}, %	5.6 [5.4]	−0.2%[b]	11.2 [8.3]	−2.9%[b]
Baseline [Current] 24-h average BP, mm Hg	127/72 [110/66]	−13%/−8%[b]	111/68 [114/70[c]]	3%/3%[b]
Night-time BP dipping, %	9.5 [9.1]	−0.4%[b]	16.6 [8.9[c]]	−7.7%[b]
Actual REE relative to predicted REE, %[d]	95%[a] [99%]	4%[b]	113%[a] [103[c]]	−10%[b]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; REE, resting energy expenditure. [a]Measurement taken at screening. [b]Absolute change is provided. [c]Measurement taken at Week 20. [d]REE was predicted based on standard height/weight/age/sex calculations.[14]

Acknowledgments: This study was sponsored by Rhythm Pharmaceuticals, Inc. Assistance with preparation of this poster was provided by Ali Rosenberg, Sherri Damlo, and Jenna Lewis, MedThink SciCom, and funded by Rhythm Pharmaceuticals, Inc.

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